64. **(New)** The expression vector of claim 62, wherein the leader sequence has no secondary structure when transcribed as RNA.

65. **(New)** The expression vector of claim 57, wherein the 3' untranslated region of the gene is modified to increase processing, export or stability of the mRNA transcribed from the gene.

66. **(New)** The expression vector of claim 57 comprising the human thyroid binding globulin promoter and the alpha-1 microglobulin/bikunin enhancer.

67. **(New)** The expression vector of claim 66 comprising two or more copies of the alpha-1 microglobulin/bikunin enhancer.

68. **(New)** The expression vector of claim 66, wherein the human thyroid binding globulin promoter and the alpha-1 microglobulin/bikunin enhancer are located upstream from the coding sequence of a gene.

69. **(New)** The expression vector of claim 68, wherein the coding sequence is also preceded upstream by a leader sequence comprising one or more introns.

70. **(New)** The expression vector of claim 69, wherein the intron comprises a consensus 5' splice donor site, and a consensus 3' splice acceptor site.

71. **(New)** The expression vector of claim 69, wherein the intron has no secondary structure when transcribed as RNA.

REMARKS

Claims 40-56 were pending in the application. Claim 40 has been amended, claim 43 has been canceled, and claims 57-71 have been added. Accordingly, following entry

of the amendments presented herein, claims 40-42 and 44-71 will be pending. For the Examiner's convenience, a copy of the claims as they will be pending upon entry of the present amendment, is provided herein as Appendix A.

Attached hereto is a marked-up version of the changes made to the claims by the current amendments, entitled "Version With Markings to Show Changes Made".

Support for the amendments to the claims can be found throughout the specification, including the claims as originally filed. For example, support for the amendment to claim 41 can be found in original claim 43. Support for the addition of new claims 57-71 can be found, for example, in original claims 40-56.

No new matter has been added. The foregoing claim amendments and cancellations should in no way be construed as an acquiescence to any of the Examiner's rejections, and have been made solely to expedite the prosecution of the application. Applicants reserve the right to pursue the subject matter of the claims prior to the amendments herein in this or a separate application(s).

Rejection of Claims 40-47 and 49-56 Under 35 U.S.C. § 102(a)

The Examiner has rejected claims 40-47 and 49-56 under 35 U.S.C. § 102(a) as being anticipated by Ill *et al.* (*Blood Coagulation and Fibrinolysis* (Dec. 1997)) and Ill *et al.* (*Thrombosis and Hemostasis* (July 1997)). Specifically, the Examiner is of the opinion that both references teach "an expression vector comprising the human thyroid binding globulin promoter, the alpha-1 microglobulin/bikunin enhancer, and a leader sequence that comprises an intron with a 5' donor site and a consensus 3' splice acceptor site all of which are upstream of the coding sequence for B-domain deleted factor VIII."

Applicants respectfully traverse this rejection and request reconsideration. The work described in the Ill *et al.* references is Applicants' own work and is unavailable as prior art under 35 U.S.C. § 102(a). In support of this assertion, Applicants submit herewith a Declaration Pursuant to 37 C.F.R. §1.132 by co-inventor Charles R. Ill that attests to the fact that the work described in Ill *et al.* (*Blood Coagulation and Fibrinolysis* (1997) 8 (S 2): S23-S30) and Ill *et al.* (*Thrombosis and Hemostasis* (1997) ISSN:0340-6245, Shattauer:Stuttgart:Abstract) was published within one year of the priority date of

the present invention, is Applicants' own work and, as such, is not available as prior art (*In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1958)).

Accordingly, Applicants respectfully request withdrawal of the instant rejection of claims 40-47 and 49-56 under 35 U.S.C. § 102(a)

Rejection of Claims 40 and 41 Under 35 U.S.C. § 102(b)

The Examiner has rejected claims 40 and 41 under 35 U.S.C. § 102(b) as being anticipated by Gould *et al.* (*J. Cell Biochem.* (1990) Suppl. 14A D432). Specifically, the Examiner states that Gould *et al.* teach an expression vector comprising the albumin liver specific promoter and the alpha-fetaprotein enhancer sequence.

Applicants respectfully traverse this rejection and request reconsideration. From the outset, Applicants respectfully note that it appears that the Examiner intended to cite Wolf *et al.* instead of Gould *et al.*, since the citation given by the Examiner (i.e., *J. Cell Biochem.* (1990) Suppl. 14A D432) corresponds to that of Wolf *et al.*, not Gould *et al.*, and because the Examiner's intended characterization of the reference corresponds to Wolf *et al.*, not Gould *et al.* Confirmation that the Examiner did in fact intend to cite Wolf et al. on the record is respectfully requested.

As amended, claim 40 is directed to an expression vector comprising a liver-specific promoter and a liver-specific enhancer, said promoter and enhancer being derived from different genes, ***wherein the liver-specific promoter is the human thyroid binding globulin promoter.*** Claim 41 further specifies that the ***promoter and enhancer are located upstream from the coding sequence of a gene.***

In contrast, Wolf *et al.* teach a retroviral vector containing an ***albumin promoter*** and an alpha-fetoprotein (AFP) enhancer sequence. The vector taught by Wolf *et al.* does not contain a human thyroid binding globulin promoter sequence as taught by Applicants. In addition, Wolf *et al.* teach that the AFP enhancer sequences are located ***downstream*** from the coding sequence of the gene of interest (see *e.g.*, line 7 of abstract). Thus, the teachings of Wolf *et al.* do not anticipate claims 40 and 41.

Accordingly, Wolf *et al.* do not anticipate the instantly claimed invention and Applicants respectfully request reconsideration and withdrawal of the rejection of claims 40-41 under 35 U.S.C. § 102(b).

Rejection of Claims 40, 41 and 45 Under 35 U.S.C. § 102(e)

The Examiner has rejected claims 40, 41 and 45 under 35 U.S.C. § 102(e) as being anticipated by Simonet *et al.* (U.S. Patent No, 6,268,212). Specifically, the Examiner is of the opinion that Simonet *et al.* "teach an expression vector comprising the liver specific albumin promoter and the liver specific HCR enhancer upstream from the coding sequence." The Examiner also states that Simonet *et al.* further teach "the placement of an intron downstream from the promoter and enhancer and upstream from the coding sequence."

Applicants respectfully traverse this rejection and request reconsideration. As set forth above, claim 40 is directed to an expression vector comprising a liver-specific promoter and a liver-specific enhancer, said promoter and enhancer being derived from different genes, ***wherein the liver-specific promoter is the human thyroid binding globulin promoter***. Claim 41 further specifies that the liver-specific promoter is the ***human thyroid binding globulin promoter*** (*e.g.*, located upstream from the coding sequence of a gene). Claim 45 further specifies that the vector comprises one or more introns located (a) downstream from the promoter and enhancer and (b) upstream from the coding sequence.

Simonet *et al.* do not teach every element of claims 40, 41 and 45. Simonet *et al.* teach an expression vector comprising the following promoters: ApoA-I, ApoA-II, ApoA-III, ApoA-IV, ApoB-100, ApoC-I, ApoC-II, ApoC-III, ApoE, albumin, alpha-feto protein, PEPCK, transthyretin, SV40, CMV and TK promoters. Simonet *et al.* do ***not*** teach a vector containing a liver specific promoter and a liver specific enhancer derived from different genes, ***let alone the human thyroid globulin promoter***. Nor do Simonet *et al.* teach a vector containing one or more introns positioned within such a vector as required by claim 45. Thus, Simonet *et al.* fail to anticipate Applicants' claimed invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 40-41 and 45 under 35 U.S.C. § 102(b).

Rejection of Claims 40-42, 45, 47 and 49 Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 40-42, 45, 47 and 49 under 35 U.S.C. §103(a) as being unpatentable over Connelly *et al.* (*Human Gene Therapy* (1996)) in view of Simonet *et al.* (U.S. Patent No. 6,268,212). Specifically, the Examiner is of the opinion that Connelly *et al.* teach an expression vector comprising the albumin liver specific promoter upstream of the coding sequence for the B-domain deleted factor VIII. . . .Simonet teaches an expression vector comprising a liver specific promoter, such as albumin, and the liver specific enhancer, HCR (hepatocyte control region)." The Examiner concludes that "[i]t would have been obvious to one of ordinary skill in the art at the time of the invention to modify the expression vector of Connelly *et al.* to include a liver specific enhancer such as the HCR enhancer taught in Simonet."

Applicants respectfully traverse this rejection and request reconsideration. As amended, the rejected claims are drawn to an expression vector comprising, in particular, the ***human thyroid globulin promoter***. Neither Connelly *et al.* nor Simonet *et al.*, even when combined in the manner suggested by the Examiner, teach or suggest such a vector. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness.

Connelly *et al.* teach a vector containing the albumin promoter, not the human thyroid globulin promoter. As acknowledged by the Examiner, Connely *et al.* also fail to teach the use of any liver-specific enhancer. Simonet *et al.* fail to make up for this deficiency since, like Connelly *et al.*, this reference fails to teach the use of the human thyroid globulin promoter, let alone in combination with a liver-specific enhancer, such as the alpha-1 microglobulin/bikunin enhancer (claim 44). Nor do these references teach the location of the promoter and enhancer, *e.g.*, upstream from the coding sequence of a gene as required by claim 41, or the location of the introns in the vector, *e.g.*, downstream from the promoter and enhancer and upstream from the coding sequence as required by claim 45. These references also do not teach that the intron in the vector comprises one

or more consensus splice sites as required by claim 47. Furthermore, these references do not teach a vector using a thyroid globulin promoter in which the 3' untranslated region of the gene of interest is modified to increase processing, export or stability of the mRNA transcribed from the gene as required by claim 49.

Accordingly, the combination of Connelly *et al.* and Simonet *et al.* fail to provide even a *prima facie* case of obviousness for the invention claimed by Applicants. Moreover, because these references do not even speak to the subject matter claimed by Applicants, e.g., use of the human thyroid globulin promoter in combination with a liver-specific enhancer in an improved vector for liver-specific gene expression, these references certainly would not have made it in any way obvious to have made or used such a vector, or have provided any reasonable expectation of success or guidance on how to do so.

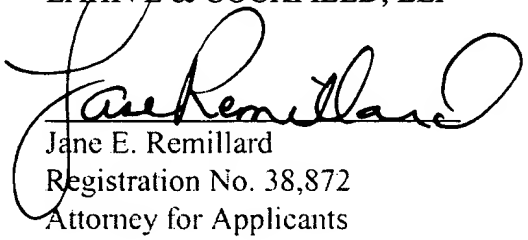
For all the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 40-42, 45, 47 and 49 under 35 U.S.C. § 103(a).

CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

LAHIVE & COCKFIELD, LLP



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Date: **March 4, 2002**

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claim 43 was cancelled.

Claim 40 was amended as follows:

40. **(Amended)** An expression vector comprising a liver-specific promoter and a liver-specific enhancer, said promoter and enhancer being derived from different genes, wherein the liver-specific promoter is the human thyroid binding globulin promoter.

Claims 57-71 were added as follows:

57. **(New)** An expression vector comprising a liver-specific promoter and a liver-specific enhancer, wherein said promoter and enhancer are derived from different genes and are located upstream from a coding sequence for a human Factor VIII protein.

58. **(New)** The expression vector of claim 57, wherein the coding sequence is expressed as a β-domain deleted human Factor VIII protein.

59. **(New)** The expression vector of claim 57, wherein the liver-specific promoter is the human thyroid binding globulin promoter

60. **(New)** The expression vector of claim 57, wherein the liver-specific enhancer is the alpha-1 microglobulin/bikunin enhancer.

61. **(New)** The expression vector of claim 57, further comprising one or more introns located (a) downstream from the promoter and enhancer and (b) upstream from the coding sequence.

62. **(New)** The expression vector of claim 61, wherein the intron is located within the leader sequence of the gene.

63. **(New)** The expression vector of claim 61, wherein the intron comprises one or more consensus splice sites.

64. **(New)** The expression vector of claim 62, wherein the leader sequence has no secondary structure when transcribed as RNA.

65. **(New)** The expression vector of claim 57, wherein the 3' untranslated region of the gene is modified to increase processing, export or stability of the mRNA transcribed from the gene.

66. **(New)** The expression vector of claim 57 comprising the human thyroid binding globulin promoter and the alpha-1 microglobulin/bikunin enhancer.

67. **(New)** The expression vector of claim 66 comprising two or more copies of the alpha-1 microglobulin/bikunin enhancer.

68. **(New)** The expression vector of claim 66, wherein the human thyroid binding globulin promoter and the alpha-1 microglobulin/bikunin enhancer are located upstream from the coding sequence of a gene.

69. **(New)** The expression vector of claim 68, wherein the coding sequence is also preceded upstream by a leader sequence comprising one or more introns.

70. **(New)** The expression vector of claim 69, wherein the intron comprises a consensus 5' splice donor site, and a consensus 3' splice acceptor site.

71. **(New)** The expression vector of claim 69, wherein the intron has no secondary structure when transcribed as RNA.